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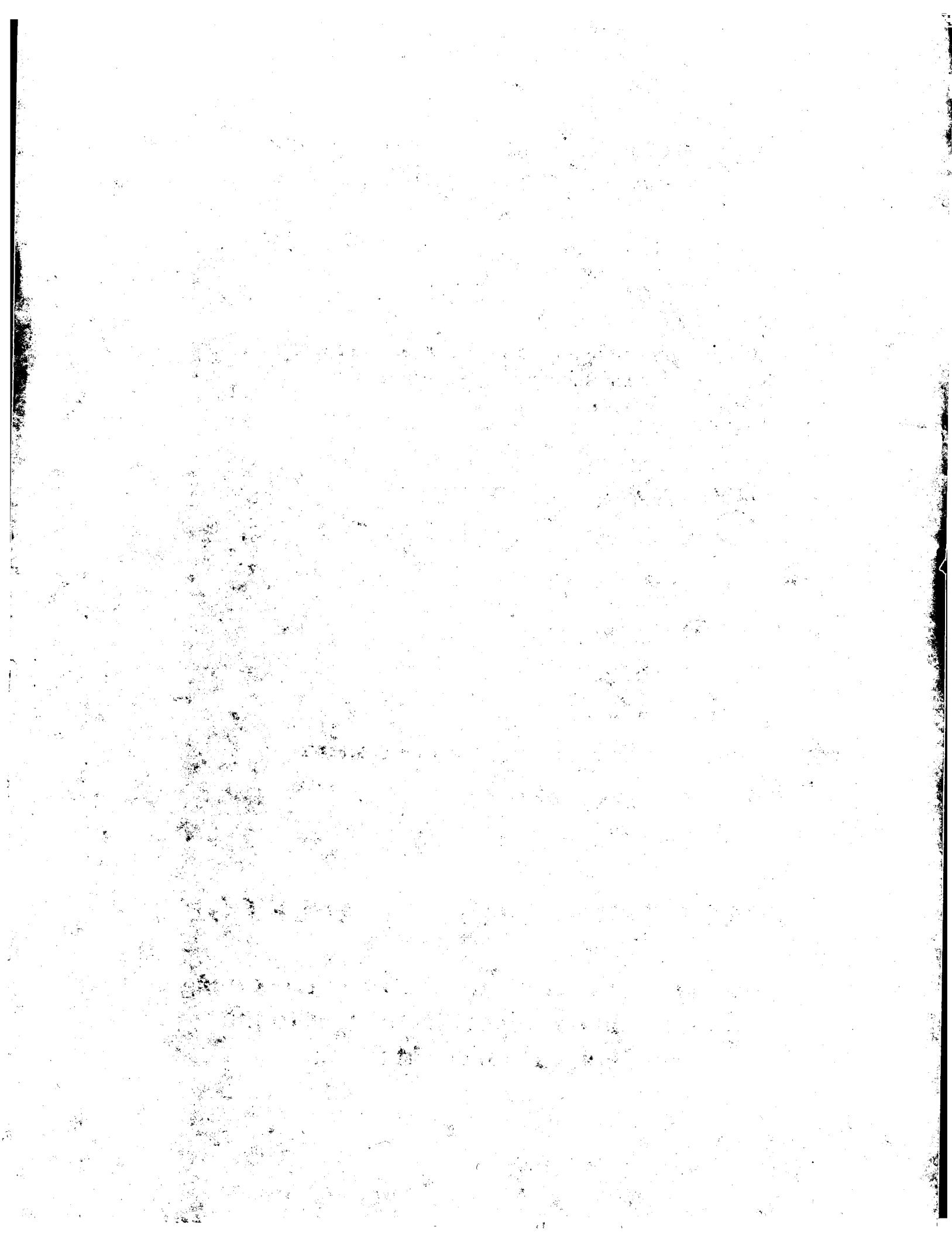
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PATENT SPECIFICATION

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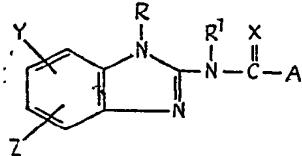
COMPLETE SPECIFICATION

Substituted Benzimidazoles and Anthelmintic Compositions containing them

We, SMITH KLINE & FRENCH LABORATORIES of 1500 Spring Garden Street, City of Philadelphia, Zone 1, Commonwealth of Pennsylvania, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to benzimidazole compounds and compositions having anthelmintic activity. In particular, the invention relates to benzimidazoles having a 2-amido group, or a thio analog thereof.

The compounds of the invention are characterized by the following structural formula:



wherein:

- A is (1) an unsubstituted or methyl substituted monocyclic 5-membered heterocyclic ring bonded to the carbonyl group through one of its carbon atoms; or
(2) straight or branched chain alkyl of 2 to 10 carbon atoms; cycloalkyl or alkyl-cycloalkyl of 3 to 10 carbon atoms; straight or

branched chain alkenyl of 3 to 10 carbon atoms; straight or branched chain alkynyl of 3 to 10 carbon atoms; naphthyl, alkylphenyl; or alkoxyphenyl; provided that when A is alkenyl or alkynyl, the double or triple bond thereof is not conjugated with the C=X double bond;

X is oxygen or sulfur;
R is hydrogen, alkyl of 1 to 10 carbon atoms, hydroxyalkyl of 1 to 10 carbon atoms, or benzyl;

R¹ is hydrogen or alkyl of 1 to 10 carbon atoms; and

Y and Z are hydrogen, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, trifluoromethyl, amino, alkylamino, dialkylamino, cyano, acylamino, halo, hydroxy, nitro, alkylthio, carboxy, carbalkoxy, carbamoyl, alkylcarbamoyl, or dialkylcarbamoyl, all the alkyl groups having 1 to 4 carbon atoms therein.

Where A is a heterocyclic group, the preferred compounds are those in which A is 2-furyl or 2-thienyl.

Other preferred compounds are those in which A is cyclopropyl, isopropyl, ethyl, propyl, or cyclobutyl; R and R¹ are hydrogen; Y and Z are hydrogen or methyl; and X is oxygen.

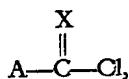
The heterocyclic nuclei embraced by formula I are those in which the hetero atoms are nitrogen, oxygen, and/or sulfur, and have a minimum of 2 carbon atoms. They include 2-furyl, 3-furyl, 5 - methyl - 2-furyl, 2-tetrahydrofuryl, 3-tetrahydrofuryl, 2-thienyl, 3-thienyl, 2-tetrahydrothienyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 4 - methyl-

[Pric]

5 - oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3,5 - dimethyl - 4 - isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 1,2,5-oxadiazol-3-yl, 1,2,5 - thiadiazol - 3 - yl, 1,2,5-thiadiazol - 4 - yl, 1,2,3 - thiadiazol - 5 - yl, 2-pyrrolyl, 3-pyrrolyl, 2-pyrrolidinyl, 2-imidazolyl, 4-imidazolyl, 1,2,3 - triazin - 4 - yl, 3-pyrazolyl, and 4-pyrazolyl.

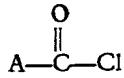
It will be apparent to those skilled in the art of organic chemistry that some of the compounds of the invention will exist in the form of optical isomers by virtue of the asymmetry at certain carbon atoms, particularly those where A is a branched chain alkyl group. It is intended that this invention include both the *d* and *l*-isomers and their racemic mixtures, the mixtures being separable by methods known to the art.

The compounds of the invention are generally prepared by condensing a 2-aminobenzimidazole with a compound of the formula



where X is as defined above, and A is a heterocyclic group as defined above, an alkyl group as defined above, a cycloalkyl or alkylcycloalkyl group as defined above, an alkenyl group as defined above; an alkynyl group as defined above; alkylphenyl, alkoxyphenyl; or naphthyl.

When a compound of the formula



is used for the condensation, the product is an amidobenzimidazole. The starting acid chlorides are obtained commercially or are prepared from the corresponding carboxylic acids by conventional methods, such methods including treatment with thionyl chloride, oxalyl chloride, and phosphorus pentachloride.

The starting 2-aminobenzimidazole may be substituted on the benzene ring, the ring nitrogen, or the exocyclic nitrogen as indicated above. The condensation of the acid chloride with the 2-aminobenzimidazole is best carried out in the presence of a base in a solvent. One preferred method of preparation utilizes one compound both as the base and the solvent. Such basic solvents include pyridine and the alkylated pyridines. A second preferred method utilizes triethylamine as a base and a mixture of tetrahydrofuran and acetone as solvent. Other base-solvent systems will be apparent to those skilled in the art of organic chemistry. The carboxylic acid chloride is preferably added dropwise to an equimolar amount of 2-amino-benzimidazole dissolved in pyridine. The solution is stirred for about 1-3 hours, and

then heated on the steam bath for a short period of time. Water is then added, or the solution is poured into ice water, to precipitate the crude product. Purification is achieved by a variety of conventional techniques including dissolving the compound in aqueous alcoholic alkali and reprecipitating with an acid such as acetic acid, by dissolving the compound in a solvent such as dimethylformamide and reprecipitating with water and/or acetonitrile, or by recrystallization from alcohols.

Compounds of formula I in which Y or Z is amino are prepared by catalytic reduction of the corresponding nitro compound, preferably using a palladium-on-carbon catalyst.

Compounds in which Y or Z is a reactive group such as carboxy or hydroxy are best prepared by a procedure which is also an alternative procedure applicable to the other compounds of the invention. Cyanamide is allowed to react with a selected carboxylic acid chloride in pyridine, triethylamine, or other base-containing solvent, and this compound allowed to react with an appropriately substituted *o*-phenylenediamine, among which are 4-hydroxy or 4 - carboxy - *o* - phenylenediamine. Upon workup, the corresponding ring-substituted products are obtained.

Compounds in which Y or Z is hydrogen, alkyl, alkoxy, chloro, bromo, trifluoromethyl, nitro, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, carbalkoxy, alkylamino, dialkylamino, cyano, acylamino, or alkylthio are prepared by either preparative route described above, i.e. by starting with the corresponding substituted *o*-phenylenediamine and condensing with the product of the reaction of cyanamide and an acid chloride, or by first preparing the ring-substituted 2-aminobenzimidazole by known methods and treating this with the acid chloride.

Compounds in which R is alkyl, hydroxylalkyl, or benzyl are prepared by starting with the appropriately substituted 2-aminobenzimidazole, and condensing it with the carboxylic acid chloride, or by alkylating or benzylating the final product with a limited amount of alkylating or benzylating agent.

Compounds in which X is sulfur are prepared by reacting the corresponding compound in which X is oxygen with phosphorus pentasulfide, preferably in a solvent.

The compounds of Formula I where R¹ is alkyl and R is hydrogen can also be prepared by treating *o*-phenylenediamine with an alkyl isothiocyanate to form an alkyl *o*-amino-phenyl thiourea. This compound is cyclized to form a 2 - alkylaminobenzimidazole, and this compound is treated with an acyl halide to yield a 2 - (N - alkylacylamino)benzimidazole.

Also part of the invention are the pharmaceutically acceptable acid addition salts which

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may be prepared in conventional manner from the basic compounds of formula I. Such salts are prepared by addition of the acid either as such or in the form of a solution to an alcoholic, acetone, or acetonitrile solution of the base. Preferred salts are the hydrochloride, hydrobromide, sulfate, phosphate, acetate, and hexamate.

The compounds of the invention have been found to possess a high degree of anthelmintic activity. They are effective against a wide variety of helminths, including *Syphacia obvelata*, *Nematospiroides dubius*, *Chabertia*, *Oesophagostomum* spp., *Trichuris ovis*, *Haemonchus contortus*, *Ostertagia* spp., *Trichostrongylus* spp., *Ascaris suum*, *Nemadirus* spp., *Cooperia* spp., and *Strongyloides papillosus*.

The amount of ingredient administered

will depend on the weight of the host, but will usually be between about 5 mg./kg. and 500 mg./kg. of body weight daily.

For example, 2-isobutyramidobenzimidazole, at an oral daily dose of 50 mg./kg., tested in mice with a natural pinworm infection, following generally the method of McCowen et al., reported in the *American Journal of Tropical Medicine*, 6, 894 (1957), cleared 96% of the worms, while at a 250 mg./kg. dose, it cleared 98%. The LD₅₀ in mice is in excess of 1 g./kg.

Additionally, compounds of this invention, at varying daily dosages of 0.0125, 0.05 and 0.20% of the mouse diet for 5 days, tested against a mouse hookworm (*N. dubius*) infection (0.2% of diet approximates 100 mg./kg. of body weight, based on 20 g. mouse) gave the results indicated in the tabulation.

| | Compound | Percent of Diet | Percent Reduction of Hookworm Burden |
|----|---|-----------------|--------------------------------------|
| 40 | 2-Propionamidobenzimidazole | 0.0125 | 10 |
| | | 0.05 | 50* |
| | | 0.20 | 78 |
| 45 | 2-Butyramidobenzimidazole | 0.05 | 0 |
| | | 0.20 | 80 |
| | 2-Isobutyramidobenzimidazole | 0.0125 | 11 |
| | | 0.05 | 71* |
| | | 0.20 | 91 |
| 50 | 2-Cyclopropanecarboxyamidobenzimidazole | 0.05 | 88* |
| | 2 - Isobutyramido - 4 - methylbenzimidazole | 0.20 | 100* |
| | | 0.05 | 85 |
| | | 0.20 | 100 |

*Figure is average of two experiments

Typical daily dosage in dogs is about 25—250 mg./kg., given orally.

In four-week old pigs, artificially infested with *Ascaris suum* larvae, 2-isobutyramidobenzimidazole was effective in markedly reducing the mean larval count per lung. Drug administration medicated diets were employed containing 0.1% of drug in the diet.

In lambs naturally infested with various gastro-intestinal nematodes, compounds of Formula I were tested at the dosages indicated below, expressed in mg./kg. of body weight, in a single dose at 10% concentration in water, with the results given in the tabulation below:

| | Compound | % Reduction |
|----|--|-------------|
| 70 | 2-Isobutyramidobenzimidazole (50 mg.) | 73.2 |
| | 2-Butyramidobenzimidazole (50 mg.) | 97.83 |
| 75 | 2-Propionamidobenzimidazole (25 mg.) | 97.3 |
| | 2-Cyclopropanecarboxamido-benzimidazole (25 mg.) | 98.9 |
| 80 | 2-Cyclobutanecarboxamido-benzimidazole (25 mg.) | 95.6 |
| | Compounds of formula I in which A is | |

a heterocyclic group, X is oxygen, and R, R¹, Y and Z are hydrogen have been found to have high activity against worms in mice and sheep at dose levels of 10—250 mg./kg. 2 - (2 - Furoylamino)benzimidazole, causes an 80—100% reduction in the number of worms present in mice infected with *Syphacia obvelata* when administered orally at a dosage level of 10—250 mg./kg. In the same test, 2 - (2 - thenoylarnino)benzimidazole caused an 84—89% reduction at a dose level of 250 mg./kg. The furoylamino compound, when administered orally to infected sheep at a dose level of 12.5 mg./kg., suspended in 80 ml. of water, eliminated 70.9% of the gastrointestinal worm burden. The compound was especially effective against *Chabertia* and *Oesophagostomum* spp. and showed good effectiveness against *Trichuris ovis*, *Haemonchus contortus*, *Ostertagia* spp., and *Trichostrongylus* spp.

The compounds are generally administered orally, as a sheep drench or a bolus for cattle. Typical drench formulations may include, in addition to the active anthelmintic compound, terra alba, tragacanth, sodium lauryl sulfate, methyl cellulose, polyethylene glycol, silicone antifoam, and water. A cattle bolus may include calcium phosphate, maize starch, talcum,

- gum arabic, and magnesium stearate. The compounds may also be formulated into a feed supplement or animal food concentrate or may be added directly to the food.
- 5 The compounds may also be formulated with a carrier into conventional dosage forms, such as capsules, liquids, or tablets.
- 10 The following examples illustrate the preparation of the compounds of the invention, but are not to be construed as limiting the scope thereof.

EXAMPLE 1**2-Propionamidobenzimidazole**

15 Ten grams of 2-aminobenzimidazole are added to 60 ml. of pyridine; the mixture is held at 0—4°C with stirring and 9.65 g. of propionyl chloride are added slowly. The reaction mixture is stirred for 10 minutes in an ice bath and allowed to stand at room temperature for one hour, followed by heating on a steam bath an additional hour. The reaction mixture is cooled and poured into approximately 3 volumes of water. The white crystalline solid which forms is collected, washed with water and dried, yielding 4.8 g. of crude product, m.p. 254.5—255.5°C.

20 The product is recrystallized twice from ethanol to give colorless crystals, m.p. 257—258.5°C. The structure of the desired product is confirmed by elemental analysis and by IR and NMR spectral data.

EXAMPLE 2**2-Isobutyramidobenzimidazole**

35 Using the procedure detailed in Example 1, 10 g. of 2-aminobenzimidazole and 8 g. of isobutyryl chloride are reacted to give 12.4 g. of crude product, m.p. 242—243.5°C.

40 Two recrystallizations from ethanol give the desired product, m.p. 243—244°C., whose structure is confirmed by elemental analysis, IR and NMR spectral data.

EXAMPLE 3**2-Butyramidobenzimidazole**

45 Using the procedure described in Example 1, 10 g. of 2-aminobenzimidazole, and 8 g. of butyryl chloride are reacted yielding 11.45 g. of product, m.p. 250—252°C, whose structure is confirmed by analytical and spectral data.

EXAMPLE 4**2-Valeramidobenzimidazole**

50 Using the procedure described in the previous examples, 10 g. of 2-aminobenzimidazole and 9 g. of valeryl chloride are reacted to give 8.25 g. of a crude product, m.p. 203—209°C.

55 The crude product is recrystallized twice from *n*-propanol. The pure product (4.7 g., m.p. 215—216°C) is dried under high vacuum over P₂O₅ and its structure confirmed by elemental analysis, and by IR and NMR spectra.

EXAMPLE 5**2-Isovaleramidobenzimidazole**

Using the procedure described above, 10 g. of 2-aminobenzimidazole and 9 g. of iso-valeryl chloride are reacted to yield 12.1 g. of a crude product, m.p. 248.5—252°C.

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The crude product is twice recrystallized from *n*-propanol in a manner similar to that previously described in Example 4, yielding 5.9 g. of purified product, m.p. 253—254.5°C. The identity of the product is confirmed by the elemental analysis, IR and NMR.

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EXAMPLE 6**2-Pivalamidobenzimidazole**

80 Using the procedure of Examples 4 and 5, a mixture of 5.32 g. of 2-aminobenzimidazole and 4.8 g. of pivaloyl chloride are reacted, washed with cold water, and dried to give 4.7 g. of a crude product, m.p. 255—256.5°C.

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The crude product is twice recrystallized from *n*-propanol. The purified product is dried as in Example 4, and submitted for elemental analysis and for IR and NMR spectra. The structure of the purified product (1.7 g., m.p. 255—256.5°C) is confirmed by the analytical and spectral data.

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EXAMPLE 7**2-Caproylaminobenzimidazole**

95 Using the procedure of the preceding example, 10 g. of 2-aminobenzimidazole and 10 g. of hexanoyl chloride are reacted, yielding 13.26 g. of a crude yellow product, m.p. 219—223°C.

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Six g. of the crude product is twice recrystallized from *n*-propanol. It is dried under vacuum to give the desired product (4.3 g., m.p. 225—226°C), confirmed by analysis.

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EXAMPLE 8**2-Heptanoylaminobenzimidazole**

105 Using the procedure of the preceding examples, 10 g. of 2-aminobenzimidazole and 11.1 g. of *n*-heptanoyl chloride are reacted to give 15.06 g. of a crude product, m.p. 204—207°C.

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The crude product is twice recrystallized from *n*-propanol. The purified product is dried *in vacuo* to give the product (9.52 g., m.p. 214—215.5°C), confirmed by analysis.

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EXAMPLE 9**2-Thioisobutyramidobenzimidazole**

115 2-Isobutyramidobenzimidazole (20.39 g.), prepared as disclosed in Example 2 above, is mixed with 200 ml. of dry dioxane. Phosphorus pentasulfide (11.19 g.) is added, and the mixture is refluxed for one hour. The reaction mixture is poured into water and neutralized to precipitate the desired thio analog of the starting material.

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EXAMPLE 10

- 5.6 g. of 2-aminobenzimidazole is added to 34 ml. of pyridine and the mixture is held at 0—4°C with 5.0 g. of cyclobutanecarboxylic acid chloride being added slowly with stirring. The mixture is then stirred at room temperature for one hour during which time a considerable amount of solid forms in the reaction solution. The mixture is poured into 5 volumes of water to precipitate a white solid, which is collected by filtration and air-dried, yielding 7.55 g. of crude product, m.p. 268—269.5°C.
- 15 The product is recrystallized twice from methanol, yielding 3.36 g. of purified product, m.p. 268.5—269.5°C. The structure of the desired product is confirmed by elemental analysis, and IR and NMR spectral data.

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EXAMPLE 11

- 2-Cyclopropanecarboxamidobenzimidazole
Using the procedure detailed in Example 10, 10 g. of 2-aminobenzimidazole and 7.84 g. of cyclopropanecarboxylic acid chloride are reacted in 60 ml. of pyridine to give 11.44 g. of crude product, m.p. 288—291°C. Two recrystallizations from *n*-propanol gives the desired product, m.p. 290—291°C, the structure of which is confirmed by elemental analysis, IR and NMR spectral data.

EXAMPLE 12

- 2 - Isobutyramido - 4 - methyl benzimidazole

Ten g. of 3 - methyl - *o* - phenylenediamine, 8.7 g. of isobutyryl chloride, and 3.44 g. of cyanamide are reacted in the following manner: the cyanamide is dissolved in 69 ml. of pyridine and the mixture is held at 0—4°C; while stirring, the isobutyryl chloride is added in portions.

The reaction mixture is maintained at 0—4°C. for 15 minutes and then kept at room temperature until complete solution is achieved.

45 10 g. of 3 - methyl - *o* - phenylenediamine is added to the reaction mixture and the resulting mixture is kept at room temperature for a few hours, and then heated on a steam bath for about 2.5 hours.

50 After cooling to room temperature, the mixture is evaporated. The resulting oil is triturated with 100 ml. of 50% water-50% ethanol to give a crystalline solid. The solid is filtered off, and sparingly washed with cold 1:1 water-ethanol.

55 This solid is suspended with stirring in 125 cc. of 1:1 water/ethanol, and treated with 5% sodium hydroxide until solution is achieved. The filtered solution is cautiously treated with glacial acetic acid until the mixture reaches pH 6.5—7.0. The white solid which appears is filtered off after cooling to about 20°C., washed with cold 1:1 water/

ethanol, and dried to give 6.26 g. of crude product.

65 The crude product is twice recrystallized from a 2:3 ethanol/water mixture giving crystalline platelets, m.p. 140—143°C. The platelets are twice recrystallized from acetonitrile, then dried to give a white crystalline solid (m.p. 142—144°C.). The structure of the desired product is confirmed by elemental analysis and by IR and NMR spectral data.

EXAMPLE 13
5 - Chloro - 2 - isobutyramido-
benzimidazole

70 Using the procedure detailed in Example 12, 13.58 g. of 4 - chloro - *o* - phenylenediamine, 10.14 g. of isobutyryl chloride and 4 g. of cyanamide are reacted to give 10.17 g. of crude product (brown powder), m.p. 228—231°C.

75 Two recrystallizations, first from 90% ethanol and then from absolute ethanol, give 2.69 g. of pure product, m.p. 232—233.5°C. The structure of the desired product is confirmed by elemental analysis, and IR and NMR spectral data.

EXAMPLE 14
5 - *n* - Butyl - 2 - isobutyramido-
benzimidazole

80 Using the procedure detailed in Example 12, 16.23 g. of 4 - *n* - butyl - *o* - phenylenediamine dihydrochloride (first converting to give 12.2 g. of the free amine), 7.88 g. of isobutyryl chloride and 3.11 g. of cyanamide are reacted to yield 6.31 g. of crude product, m.p. 125—128°C. The crude product is dissolved in 50 ml. of ethanol while heating on a steam bath. The solution is filtered and water is slowly added until a slight opalescence is present, followed by crystallization with increasing water addition. The crystals are cooled, washed and air-dried, yielding 4.3 g. of the desired product (m.p. 128—133°C.), whose structure is confirmed by elemental analysis, IR and NMR spectral data.

EXAMPLE 15
2-(2-Ethylcaprolylamino)benzimidazole

110 Ten g. of 2-aminobenzimidazole and 12.1 g. of 2-ethylhexanoyl chloride are reacted in the following manner. To a solution of the 2-aminobenzimidazole in 60 cc. of dried pyridine is added the acid chloride while cooling the pyridine solution at 10°C. The mixture is stirred at 0°C. for 20 minutes, then at room temperature for 40 minutes. It is then poured into 500 ml. of water, giving an oil which is extracted three times with 200 cc. of benzene. The combined benzene extracts are washed with several portions of water. The benzene solution is evaporated to an oil, which oil is dissolved in acetonitrile, then ethereal HCl is added until the solution is

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red to litmus paper. Scratching the vessel initiates crystallization. The crystals are cooled, filtered off, washed with cold acetonitrile and dried. The solid is placed in 100 cc. of ethanol, followed by the addition of sufficient water to cause solution. The solution is filtered during which time a solid crystallizes out. The solid is cooled, filtered off, and dried, yielding the HCl salt of the desired product (10.7 g.), m.p. 183—186.5°C.

The free amine is obtained by placing the hydrochloride salt in alcohol and then adding aqueous ammonia until slightly alkaline. The free base slowly becomes crystalline from the initial gum that forms. Solid is filtered off and dried. Part is recrystallized again from ethanol, yielding 6.7 g.

This latter product is recrystallized from acetonitrile with white crystals forming slowly from the solution. The crystals are filtered off, washed with cold fresh acetonitrile, and dried to give 5.1 g. of product, m.p. 125—129°C.

EXAMPLE 16

2-(N-methylpropionamido)benzimidazole
75.6 g. (0.7 moles) *o*-phenylenediamine is dissolved in 500 ml. of ethyl acetate at 65—70°C. Some dark insoluble material (presumably a contaminant of the starting material) is filtered off. The solution is stirred at 60°C. and 51 g. (47.7 ml.=0.7 moles) of methyl isothiocyanate is added in portions. After about 3/4 of the isothiocyanate is added, the temperature rises rapidly to reflux. The rest of the isothiocyanate is added very slowly and the mixture is kept at 75—80°C. for 15 minutes. It is then seeded and chilled. The thiourea is collected, washed with ethyl acetate, and air-dried to yield 87 g., m.p. 140°C. with decomposition and solidification.

60 g. of yellow mercuric oxide is stirred in 300 ml. of ethanol at 65°C. The thiourea is added in portions, fairly quickly. The mercuric oxide darkens and the temperature rises to 73°C. The mixture is stirred at 73°C. for 10 minutes. The solids are filtered off and an additional 30 g. of mercuric oxide is added. The mixture is stirred at 50—60°C. for 15 minutes. The mercury salts are filtered off, and the ethanol is evaporated *in vacuo*. The resulting solid is dissolved in 100 ml. water and dilute HCl. Darco charcoal is added and the mixture is filtered. The word "Darco" is a Trade Mark. The clear solution is adjusted to pH 8—9 with aqueous ammonia and a heavy precipitate forms after cooling. The solid 2-methylaminobenzimidazole is collected, washed with cold water, and air dried to give 9 g., m.p. 188—191°C.

An analytical sample is recrystallized from acetonitrile to constant m.p. of 190—192°C.

1.5 g. (.01 moles) of 2-methylaminobenzimidazole is dissolved in about 10 ml. dry pyridine. The solution is cooled in an ice bath and 0.65 g. (0.007 moles) of propionyl

chloride is added in 2 portions. After about one minute, white solid appears. The mixture is refluxed for 4 hours. The clear solution is cooled slightly, and the pyridine evaporated. 40 ml. of water is added and a white solid collected, washed with water and dried to give 0.9 g., m.p. 178—181°C.

The product is completely soluble in aqueous alkali and can be reprecipitated by the addition of acetic acid to pH of 7.5. The analytical sample is recrystallized from ethanol/water, m.p. 179—181°C.

EXAMPLE 17

2-Isobutyramido-5-nitrobenzimidazole
14.57 g. of 4 - nitro - *o* - phenylenediamine, 5.06 g. of isobutryl chloride, and 2 g. of cyanamide are reacted in the following manner: The cyanamide is dissolved in 40 ml. of pyridine and the mixture is held at 0—4°C. while stirring. The isobutryl chloride is added, and the reaction mixture is maintained at 0—4°C. for 15 minutes, then at room temperature for 35 minutes, during which time all of the solid dissolves.

The 4 - nitro - *o* - phenylenediamine is added to the reaction mixture at room temperature over a 35 minute period. The resulting reaction mixture is heated on a steam bath for about 2 1/2 hours, followed by the addition of 40 ml. of water, causing the formation (upon scratching) of a solid. The solid is removed by filtration.

The filtrate is evaporated to dryness and the solid is suspended in 50 ml. of 50% aqueous ethanol. Then 25 ml. of 2.5N sodium hydroxide is added and the mixture manually shaken for several minutes. After filtration, the filtrate is neutralized with glacial acetic acid, whereupon a solid precipitates, oily at first, solidifying upon scratching. This alkali soluble fraction is collected, washed with aqueous ethanol, and dried to give 5.03 g. of product.

The product is suspended in 35 ml. of 50% aqueous ethanol and 10% sodium hydroxide is added, the insoluble material being filtered off. The filtrate is neutralized to precipitate a solid, which is to give 3 g. of product, m.p. 224.5—227°C.

The product is recrystallized from ethanol (65 ml.) and is charcoaled. It is cooled, collected, washed, and dried. The dried solid is again recrystallized from about 50 ml. of absolute ethanol, and is dessicated, yielding 0.354 g. of pure product, m.p. 227—230°C. The structure of the desired product is confirmed by elemental analysis and by IR and NMR spectral data.

EXAMPLE 18

2 - Cyclopropanecarboxamido - 4 - tri-fluoromethylbenzimidazole
22 g. of 4 - trifluoromethyl - *o* - phenylenediamine, 13.1 g. of cyclopropanecarboxylic

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acid chloride, and 5.2 g. of cyanamide are reacted in the following manner: The cyanamide is dissolved in 100 ml. of pyridine and the mixture is cooled with stirring. The acid

- 5 chloride is added portionwise with stirring and cooling. After the addition, the mixture is stirred at 0.4°C. for about 10 minutes, and then at room temperature for 1 hour.

- 10 The diamine is added portionwise, causing a slightly exothermic reaction. The reaction mixture is stirred at room temperature for about 30 minutes, then on a steam bath for about 2 1/2 hours.

- 15 To the resulting mixture about 200 ml. of water is added slowly and the mixture is stirred for about 30 minutes and cooled. The precipitate is collected and washed with water and the solid is dried to give 11.5 g. crude product, m.p. 243—247°C. The product is recrystallized from about 450 ml. of ethanol plus 350 ml. water, and is cooled overnight.

- 20 The precipitate is collected and washed with 2:1 water-ethanol to give 8.9 g., m.p. 249—252°C.

- 25
- EXAMPLE 19**
2-(2-Furoylamino)benzimidazole
2-Aminobenzimidazole (10.0 g., 0.075 moles) is dissolved in 60 ml. of dry pyridine and the solution cooled in ice. To this stirred and cooled solution is added dropwise 9.75 g. (0.075 moles) of furan-2-carboxylic acid chloride over a 25 minute period. The mixture is stirred with cooling for 15 minutes, then at room temperature for about two hours, and then 200 ml. of water is added. After the mixture is cooled, the resulting solid is filtered off and dried. The crude product is placed in 400 ml. of 1:1 water-ethanol and sufficient 10% sodium hydroxide added to achieve solution. The solution is filtered through Super-Cel and the filtrate neutralized to pH 6.0. The word "Super-Cel" is a Trade Mark. The resulting solid is filtered off, washed with 1:1 water-ethanol, and dried. The compound is recrystallized by dissolving in a minimum of dry dimethylformamide and adding dry acetonitrile to the filtered warm solution until turbidity is reached. Cooling produces crystallization. A second recrystallization, followed by extraction with hot water and drying gives the pure title product, m.p. 318—320°C. dec.

- 30
- Calc'd. for $C_{12}H_9N_3O_2$:
C, 63.43; H, 3.99; N, 18.49%.
Found:
C, 63.57; H, 3.97; N, 18.51%.

- 35
- To a methanol suspension of the product is added ethereal hydrogen chloride until the solution is red to litmus. The solution is cooled and scratched to give crystals of the

40 product hydrochloride, which are collected and purified by recrystallization.

EXAMPLE 20

2-(2-Thenoylamino)benzimidazole 65

Thiophene - 2 - carboxylic acid (50 g., 0.39 moles) and thionyl chloride (130 ml.) are warmed with stirring on a steam bath for about one hour. The excess thionyl chloride is then removed by distillation at atmospheric pressure. The acid chloride is distilled *in vacuo* at 82—84°C./ca. 20 mm.

70 The acid chloride (25 g., 0.17 moles) is added dropwise over a 15 minute period to a solution of 22.8 g. (0.17 moles) of 2-aminobenzimidazole in 140 ml. of dry pyridine. The mixture is stirred for an additional 15 minutes and then maintained at 65—75°C. for a half hour. The solution is poured into a 4-fold excess of ice water and the solid collected and washed with water. The solid is suspended in 400 ml. of 50% ethanol, and 10% sodium hydroxide is added until all the solid has dissolved. After the solution is filtered, acetic acid is added to pH 7.5, and the resulting solid collected. The solid is dissolved in dimethylformamide at steam bath temperature, the solution is filtered, and water is added until the cloud point is reached. After cooling, the precipitated material is collected and then boiled in water to remove any residual dimethylformamide. The insoluble title product is filtered off. The compound melts at 308—309°C.

EXAMPLE 21
2 - (2 - Pyrrolecarboxamido)benzimidazole 90

95 To 8.2 g. (0.0394 moles) of finely divided phosphorus pentachloride suspended in 30 ml. of chloroform (dried over P_2O_5) and cooled in an ice bath is added in small portions over one half hour 4 g. (0.036 moles) of 2-pyrrolecarboxylic acid with stirring. During the course of the addition, the solution becomes thick and later is fluid. The chloroform is removed at room temperature under vacuum. To the resulting black residue is added 40 ml. each of ether and dry petroleum ether (30—60°C.), in that order, and the solution then filtered. The solvent is removed under vacuum at a temperature lower than 20°C. The ether-petroleum ether addition, filtration, and evaporation procedure is then repeated, except that about one-fourth of the solvent is left. Upon cooling, solid is formed and collected, and then washed with cold petroleum ether. Evaporation of the filtrate gives more of the material, which is the acid chloride.

100 The acid chloride (0.95 g., 7.3 mmoles) is dissolved in 10 ml. of dry tetrahydrofuran and added dropwise to a solution of 0.98 g. (7.3 mmoles) of 2-aminobenzimidazole in 30 ml. of 5:1 acetone-tetrahydrofuran and 2 ml.

(1.48 g., 14.6 mmoles) of triethylamine. The mixture is stirred at room temperature for 1 hour, the resulting solid removed, and *ca.* 150 ml. of water is added to the filtrate. 5 Freezing the filtrate gives a brown solid which is collected on thawing and suspended in *ca.* 10 ml. of 50% ethanol. Sodium hydroxide (10%) is added until the solution is strongly basic. The insoluble material is then collected 10 and the filtrate acidified to *ca.* pH 7 with 3N HCl. The resultant precipitate is filtered off and washed with 50% ethanol. The compound is dissolved in dimethylformamide at steam bath temperature, the solution filtered, 15 and water added until a precipitate forms. The mixture is cooled and the precipitate collected and dried to give the title product, m.p. 316—317°C. dec.

EXAMPLE 22

20 5 - Amino - 2 - cyclopropanecarbox-
amidobenzimidazole

A solution of 5 - nitro - 2 - cyclopropane-carboxamidobenzimidazole in formic acid is hydrogenated over 5 percent palladium-on-carbon. When hydrogen uptake is complete, the solvent is removed *in vacuo*, the residue diluted with water, and the product collected after neutralization to pH 6.

The hydrochloride salt is prepared by 30 evaporating a solution of the free amino compound in dilute hydrochloric acid to dryness.

EXAMPLE 23

25 5(6) - Carboxy - 2 - (2 - furoyl-
amino)benzimidazole

Cyanamide (3.44 g.) is dissolved in 70 ml. of pyridine and the mixture is cooled to 0—4°C.; while stirring, 10.7 g. of furan-2-carboxylic acid chloride is added in portions. The reaction mixture is maintained at 0—4°C. 40 for 15 minutes, and is then allowed to stand for a short period at room temperature.

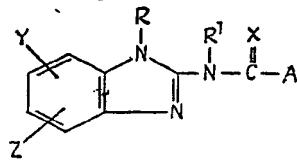
4 - Carboxy - *o* - phenylenediamine (12.5 g.) is added and the resulting mixture is kept at room temperature for a few hours, and 45 then heated on a steam bath for about 2.5 hours.

The pyridine is evaporated *in vacuo*, aqueous alcohol is added, and the mixture is carefully acidified with dilute hydrochloric acid 50 to precipitate the crude product.

The product is then purified by recrystallization.

WHAT WE CLAIM IS:—

1. A compound of the formula



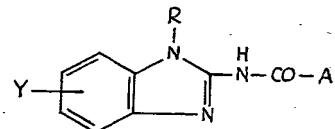
where A is (1) an unsubstituted or methyl substituted monocyclic 5-membered heterocyclic ring bonded to the carbonyl group through one of its carbon atoms; or
 (2) straight or branched chain alkyl of 2 to 10 carbon atoms; cycloalkyl or alkylcycloalkyl of 3 to 10 carbon atoms; straight or branched chain alkenyl of 3 to 10 carbon atoms; straight or branched chain alkynyl of 3 to 10 carbon atoms; naphthyl; alkylphenyl; or alkoxyphenyl; provided that when A is alkenyl or alkynyl, the double or triple bond thereof is not conjugated with the C=X double bond;

X is oxygen or sulfur;
 R is hydrogen, alkyl of 1 to 10 carbon atoms, hydroxyalkyl of 1 to 10 carbon atoms, or benzyl;

R¹ is hydrogen or alkyl of 1 to 10 carbon atoms; and

Y and Z are hydrogen, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, trifluoromethyl, amino, alkylamino, dialkylamino, cyano, acylamino, halo, hydroxy, nitro, alkylthio, carboxy, carbalkoxy, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, all of the undefined substituent alkyl groups having 1 to 4 carbon atoms therein; or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula



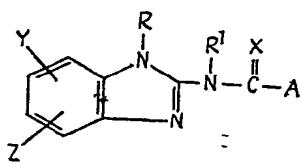
where Y is hydrogen, alkyl or alkoxy of 1 to 10 carbon atoms, chloro, bromo, trifluoromethyl, hydroxy, nitro, carboxy, carbamoyl, carbomethoxy, or dimethylamino;

R is hydrogen, alkyl of 1 to 10 carbon atoms, or benzyl; and

A is an unsubstituted or methyl substituted monocyclic 5-membered heterocyclic ring bonded to the carbonyl carbon atom through one of its carbon atoms;

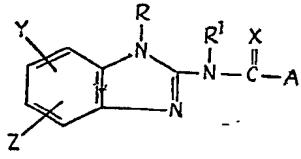
or a pharmaceutically acceptable acid addition salt thereof.

3. A compound of the formula



where A is a straight or branched chain alkyl of 2 to 10 carbon atoms; straight or branched chain alkenyl of 3 to 10 carbon atoms; or straight or branched chain alkynyl of 3 to 10 carbon atoms; provided that when A is alkenyl or alkynyl, the double or triple bond thereof is not conjugated with the C=X double bond;
 5 R is hydrogen, alkyl of 1 to 10 carbon atoms, or hydroxyalkyl;
 10 R¹ is hydrogen or alkyl of 1 to 10 carbon atoms;
 15 X is oxygen or sulfur; and
 20 Y and Z are hydrogen, alkoxy of 1 to 10 carbon atoms, trifluoromethyl, amino, alkylamino, dialkylamino, cyano, acylamino, halo, hydroxy, alkylthio, carboxy, carbalkoxy, carbamoyl, alkylcarbamoyl, or dialkylcarbamoyl, all of the undefined substituent alkyl groups having 1 to 25 4 carbon atoms.

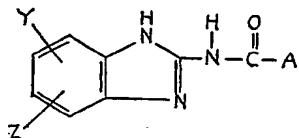
4. A compound of the formula



where A is cycloalkyl or alkylcycloalkyl of 3 to 10 carbon atoms;
 30 X is oxygen or sulfur;
 R is hydrogen, alkyl of 1 to 7 carbon atoms, or hydroxyalkyl of 1 to 7 carbon atoms;
 35 R¹ is hydrogen or alkyl of 1 to 10 carbon atoms; and
 Y and Z are hydrogen, straight or branched chain alkyl of 1 to 10 carbon atoms, straight or branched chain alkoxy of 1 to 10 carbon atoms, trifluoromethyl, amino, alkylamino, dialkylamino, acylamino, halo, hydroxy, alkylthio, carboxy, carbalkoxy, carbamoyl, alkylcarbamoyl, or dialkylcarbamoyl, all of the undefined sub-

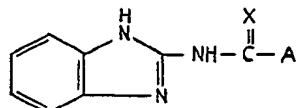
stituent alkyl groups having 1 to 45 4 carbon atoms.

5. A compound of the formula



where Y and Z are hydrogen, methyl, methoxy, chloro, or trifluoromethyl; 50 A is alkyl of 3 to 7 carbon atoms, cycloalkyl of 3 to 10 carbon atoms, or furyl.

6. A compound of the formula



55

where X is oxygen or sulfur, and

A is alkyl of 3 to 7 carbon atoms.

7. 2-Propionamidobenzimidazole.

8. 2-Butyramidobenzimidazole.

9. 2-Isobutyramidobenzimidazole.

10. 2-Cyclopropanecarboxamidobenzimidazole.

11. 2-(2-Furoylamino)benzimidazole.

12. 2 - Cyclobutanecarboxamidobenzimidazole.

13. 2 - Isobutyramido - 4 - methyl - benzimidazole.

14. A compound as claimed in claim 1 in which X is oxygen, and R, R¹, Y, and Z are hydrogen.

15. An anthelmintic composition comprising 2 - cyclopropanecarboxamidobenzimidazole and a nontoxic pharmaceutical carrier.

16. An anthelmintic composition comprising 2 - (2 - furoylamino)benzimidazole and a nontoxic pharmaceutical carrier.

17. An anthelmintic composition comprising a compound as claimed in Claim 1 and as disclosed in Examples 1—23 and a non-toxic pharmaceutical carrier therefor.

18. An animal feed containing a compound as claimed in Claim 1.

HASELTINE, LAKE & CO.,
 Chartered Patent Agents,
 28, Southampton Buildings,
 Chancery Lane, London, W.C.2.
 Agents for the Applicants.

